Gynecologic Cancers

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Introduction

Tremendous advances are being made in the treatment of gynecologic cancers today. Some of these advances are being made right here in Hawaii. Gynecologic cancer, including ovarian, fallopian tube, primary peritoneal, cervical, vaginal, vulvar, endometrial, uterine sarcoma, and gestational trophoblastic disease strike more than 100,000 women a year in the United States resulting in tens of thousands of potentially preventable deaths. Exciting advances are occurring in cancer surgery, chemotherapy, radiotherapy, and the biological understanding of these cancers. This paper will review the basics of the major cancers: ovarian, cervical, and endometrial and touch on some exciting new advances.

Ovarian Cancer

Ovarian carcinoma is the second most common gynecologic malignancy in the United States. Each year, ovarian cancer strikes 26,000 women killing an estimated 14,000. This represents 55% of all deaths from gynecologic cancers, making ovarian cancer the most lethal gynecologic malignancy.

Epithelial ovarian tumors originate from coelomic epithelial cells that cover the ovary and account for approximately 65% of all ovarian cancers. Germ cell cancers and stromal cell cancers account for the remaining proportion of ovarian cancer. Epithelial tumors may be benign, "borderline" (low malignant potential), or malignant. The invasive epithelial cancers have a peak age incidence between 55 and 65, although patients can be diagnosed from 10 to 100.

When considering ovarian cancer, most people refer to the most common and most deadly type: epithelial. Two other epithelial ovarian-like cancers are fallopian tube and primary peritoneal, which do not originate in the ovary, but are biologically virtually identical.

Ovarian cancer frequently involves the omentum and/or retroperitoneal lymph nodes with pleural effusions or parenchymal liver metastasis. Approximately 70% of women present with advanced Stage III and IV disease and have a median survival rate of less than 25%. The overall survival for all epithelial ovarian cancer is 50%.

The survival rate for local, regional, and distant stage disease is similar between ovarian carcinoma and breast carcinoma. However, the overall survival for women with ovarian cancer is substantially less than for those women with breast cancer due to the preponderance of late stage ovarian cancers. Unlike mammography in breast cancer, there is no effective screening test for ovarian cancer. Combine this with few specific early symptoms, and it is understandable why most women with ovarian cancer are diagnosed with Stage III and IV disease.

Only a few factors have been linked to an increased risk for the development of ovarian cancer. These include increasing age, family history of breast or ovarian cancer, personal history of colon or breast cancer, and nulliparity. Really, we don't know what causes this disease. On the other hand, the risk of developing ovarian cancer is reduced by 60% with five years of oral contraceptive use. The protective effect of oral contraceptive use appears to be long-term. In addition, pregnancy also reduces ovarian cancer risk, as does tubal ligation and breast-feeding.

For women in the general population without a family history of ovarian cancer, the lifetime risk is about 1 in 60 or 1.6%. If a woman has one first-degree relative (mother or sister) with ovarian cancer, that risk increases to 1 in 20 or 5%. If there are two first-degree relatives with ovarian cancer, that risk increases to 1 in 14 or 7%. Add in early age and that risk is even higher. Women who are members of a family with a hereditary ovarian cancer syndrome have a lifetime risk of developing ovarian cancer as high as 40%. Women with a known BRCA1 or BRCA2 germ line mutation have a 35% to 65% risk of developing ovarian cancer in their lifetime and an even higher risk of developing breast cancer.

Hereditary ovarian cancer accounts for 10% of epithelial ovarian carcinomas. In addition to the BRCA1 and BRCA2 gene-related breast/ovarian cancer syndromes, HNPCC (Hereditary Non-Polyposis Colorectal Cancer) is another important cancer syndrome worthy of mention. This hereditary syndrome, caused by a mutation in the mismatch repair genes, increases the risk of not only colon cancer, but also endometrial and ovarian cancer.

One strategy to reduce the risk of dying from ovarian cancer is the use of oral contraceptive pills for chemoprevention. Recent data suggests that the progestational component of the pill may increase ovarian epithelial apoptosis, resulting in a lowered risk. Another strategy is prophylactic oophorectomy, which dramatically reduces the risk of developing ovarian cancer. However, even with oophorectomy, primary peritoneal carcinoma can occur in 3% of cases.

Unfortunately, there is no screening strategy available currently that is sensitive and specific enough to offer to the general population. In high-risk populations, CA-125 and transvaginal ultrasonography may detect cancers earlier, but this is unproven.

CA-125 is a serum tumor marker that is elevated in 70% of women with advanced epithelial ovarian carcinoma. CA-125 is an antibody to the OC-125 antigen found on many mesothelial surfaces. Although elevated in advanced disease, CA-125 has not been shown to be an effective screening tool because it is elevated in only 25% to 50% of Stage I cancers. Furthermore, because CA-125 is elevated in so many other nonmalignant conditions like endometriosis, pelvic inflammatory disease, pregnancy, liver and renal disease, it is not reliable even if it is elevated. For this reason, CA-125 should not be used as a screening test in the general population.

Ultrasound also has been advocated as a screening test for ovarian cancer. Unfortunately, both transabdominal and transvaginal ultrasound have a high false-positive rates. In one study, 5,000 women were screened with ultrasound. Sixty-five laparotomies were neces-

sary in order to detect one case of early ovarian cancer. In a subsequent study of 1,200 women who had a strong family history of ovarian cancer and who underwent transvaginal ultrasound screening, there were 12 exploratory surgeries for every case of ovarian cancer. Current research aims at developing a more precise ability to distinguish benign tumors from those that are malignant by combining a variety of screening modalities.

Newer screening methods are currently being investigated. Serum lysophosphatidic acid (LPA) and a novel protein marker panel are two blood marker detection methods that are currently in early trials but appear very promising. Because early ovarian cancer is highly curable, it is worthwhile to continue searching for a better screening method. We are currently formulating an ovarian cancer screening trial here in Hawaii.

Contrary to what is commonly accepted, women with ovarian carcinoma do have symptoms. In a recent study of over 1,700 women with all stages of epithelial ovarian cancer, over 90% reported that they had symptoms for a duration of 1-12 months prior to their diagnosis. The problem with ovarian cancer symptoms is that they are vague and generally not gynecologic. The most common symptoms reported are abdominal bloating with increased abdominal girth, fatigue, and gastrointestinal disturbances, especially constipation, diarrhea, early satiety, urinary symptoms, abdominal and pelvic pain, and menstrual irregularities.

Patients who present with abdominal, GI, GU, or gynecologic complaints deserve a pelvic exam as part of a complete physical evaluation. Making the diagnosis of ovarian cancer can be challenging because the vague signs and symptoms, but an early diagnosis can improve a chance at a cure. Ultrasounds and CT scans are the best studies to identify a mass or ascites; however, they are currently unable to definitively distinguish benign from malignant neoplasms. A CA-125, when elevated, would indicate a higher likelihood that an ovarian tumor is malignant, especially in a post-menopausal woman. It is not appropriate to aspirate a mass or open a mass in the abdominal cavity because of the danger of seeding the abdomen with clonogenic cancer cells. In general, any patient with a suspicious ovarian mass or unexplained ascites with or without an elevated CA-125 should be referred to a gynecologic oncologist for specialty care.

Appropriate surgical staging in ovarian cancer is essential to determine the appropriate choice of adjuvant therapy. One-third of patients with presumed Stage I disease will be found to actually have Stage III disease when the appropriate staging operation is performed. In advanced disease, maximal surgical cytoreduction translates into improved survival. Our recently published data demonstrates that improved survival was seen in ovarian cancer patients who had a gynecologic oncologist involved in their care. This improved survival is most likely due to the gynecologic oncologist's familiarity with the disease and his or her extensive surgical training directed at being able to remove as much cancer as possible. Unfortunately, the majority of women who present with ovarian cancer will have extensive pelvic and intra-abdominal disease. For these women, removal of all gross disease is considered optimal and is associated with a significant survival advantage. Median survival and cure rates following optimal cytoreduction are almost double that of women in whom the surgeons could not remove all gross disease and achieve an optimal result. Cytoreduction for advanced disease often requires removal of large pelvic tumors with en bloc resection of the uterus, ovaries, and recto sigmoid; resection of large omental tumor cakes; small bowel resection; and removal of extensive diaphragmatic and peritoneal implants. Significant surgical expertise and special training are required to perform radical ovarian cancer cytoreductive procedures.

Most patients with ovarian cancer require adjuvant chemotherapy after initial surgery. Results from cooperative group trials (i.e., Gynecologic Oncology Group, Southwest Oncology Group) have found that the best initial chemotherapy for ovarian cancer is Carboplatin plus Taxol. We have now opened the GOG here in Hawaii, allowing our patients the opportunity to be enrolled in trials offering new medications and novel combinations of existing chemotherapies with the hopes of improving survival.

GOG 182 offers triplet therapy and sequential double therapy with Platinum, Taxol, Gemcitabine, Topetecan and Doxil as upfront therapy. Another trial we have brought to Hawaii adds gamma-interferon to upfront therapy. Although most patients with advanced initial disease will achieve a complete clinical response after surgery and chemotherapy, patients with advanced (Stage III and IV) ovarian cancer have a very high recurrence rate approaching 80%. Treatment options for recurrent disease include a secondary cytoreductive surgery, retreatment with platinum and Taxol where retreatment responses can be as high as 50%, or multiple second-line therapies including Topetecan, Doxil, Etoposide, Gemcitabine, Hexalen, Ifosomide, Vinorelbine, Tamoxifen, or Herceptin. Participation in clinical trials evaluating second-line agents is now available here in Hawaii.

Cervical Cancer

Approximately 13,000 women in the United States develop cervical cancer each year, resulting in 5,000 deaths. Cervix cancer is the most common and deadly cancer for women world wide. Fortunately though, as a result of wide-spread cancer screening with the pap smear, cervix cancer deaths in the United States are a fraction of what they were just 50 years ago.

The risk factors for cervical cancer are well known. Most of them are associated with risk factors for contracting a sexually transmitted disease. Women who begin intercourse at an early age are at a higher risk. Those who have had multiple sexual partners or have a partner who themselves have had several partners place themselves at higher risk. Smoking is also a strong a risk factor as is lower socioeconomic status and a history other of sexually transmitted diseases.

Cervical cancer is a sexually transmitted disease and the human papilloma virus (HPV) is the causative agent. While up to 50% of the United States population is infected with HPV, only a small minority ever develop cervical lesions. This is because only a handful of high-risk types lead to cancer. The great majority of women infected with HPV will never develop cancer.

The pap smear is a screening test for cervical cancer that detects abnormalities in the cervical cells caused by HPV infection. A woman should have her first Pap test and pelvic exam at the age of 18 or after the first onset of intercourse, whichever comes first. If a woman is in a low-risk category after three consecutive, normal annual examinations, the Pap test may be performed somewhat less frequently. However, if either the woman or her male partner is in

a high-risk category, the Pap test should be continued to be performed on an annual basis for a lifetime. In today's society, most women are considered to be at risk.

The Pap smear is not a completely accurate test. For any single Pap smear, the false-negative rate is 20%. Fortunately, the latency period for a precancerous lesion to develop into invasive cancer of the cervix, while variable, is usually measured in years. Regular screening of the cervix should identify a pre-malignant cervical lesion, which may be effectively and simply treated by a specialist in the area. Of note, half of the women with cervical cancer have never had a Pap smear, and one quarter of the cases (41%) of the deaths occur in women 65 years of age or older. It is important to note that women who are postmenopausal still require Pap smear screening yearly. Newer methods of screening are currently being investigated. One approach is the detection of a high-risk vaginal HPV infection as a prediction of likelihood to develop cervical cancer. Currently, HPV screening is only useful in the context of a mildly abnormal (ASC-US) Pap smear.

Despite the limitations of a Pap smear, three yearly Pap smears will lower the risk of dying from cervical cancer by over 90%. Abnormal Pap smears result in colposcopic evaluation and directed cervical biopsy. In some cases, pre-malignant disease can be followed over time. Other more extensive pre-malignant disease is treated with cryotherapy, laser vaporization, cervical conization, hysterectomy or more commonly, LEEP.

For women diagnosed with invasive cancer, the signs and symptoms may be silent until there is advanced disease. Some women may report postcoital bleeding, a foul vaginal discharge, or other abnormal bleeding. Signs of advanced cancer may be pelvic pain, unilateral leg edema or pain. A pelvic mass or grossly visible cervical lesion may also be noted.

Patients diagnosed with invasive cervical cancer should be referred to a gynecologic oncologist. Very early disease in selected patients who desire preservation of fertility can be treated conservatively with a cervical conization or radical trachelectomy. Surgical care of advanced local disease is accomplished with radical hysterectomy and pelvic lymphadenectomy.

For those cancers that are too large for radical hysterectomy or ones that have spread beyond the cervix, chemoradiation therapy is the treatment of choice. Recent studies have shown that a combination of radiation plus cisplatin offers the best hope for women with advanced cervical cancer. External beam radiation targets both the primary tumor and the other pelvic tissues, including the pelvic lymph nodes. This is followed by two or more radiation cervical implants, also known as brachytherapy. It has been recently demonstrated that the use of concurrent cisplatin-based chemotherapy with radiation significantly improves the chances of survival by acting as a radiation sensitizer and also decreasing the chance of distant spread.

Pre-malignant cervical disease, dysplasia, has a nearly 100% five-year survival. Early invasive disease is highly curable with radical surgery or radiotherapy and five-year survival rates are nearly 90%. Unfortunately, distant disease is virtually incurable. Clinical trials utilizing newly developed drugs are currently available in Hawaii. In addition, there are now HPV therapeutic vaccinations designed to stimulate the immune system against metastatic disease in early trials.

The management of recurrent cervical cancer is problematic. For those women who have not received primary radiation as initial therapy, chemoradiation may be curative or palliative. An occasional isolated soft-tissue recurrence may be treated by resection with long-term survival. The use of chemotherapy is palliative in nature and has relatively little impact on the length and quality of life.

Vulvar and vaginal cancer, although uncommon, are easily treatable if caught early. Both are similarly thought to be caused by the HPV virus.

Promising research is now under way in the field of cervical cancer prevention. The most exciting work involves the development of a vaccine against the human papilloma virus. Vaccines are being designed for both prophylaxis and therapy. At the University of Hawaii, we have opened a new HPV vaccine trial for the prophylaxis of HPV infections. To be enrolled, women must not have been infected with the HPV virus. If this trial is successful at preventing HPV infection, it will have the most significant impact in history on cancer prevention. Of critical importance is to encourage participation of women with cervical cancer and other malignancies in clinical trials. Adult participation in clinical trials is currently less than 5% across the nation. If we are to make any progress against this disease, development of new treatments, and hence, clinical trial participation is absolutely essential.

Endometrial Cancer

Endometrial cancer is the most common pelvic malignancy in the United States affecting nearly 40,000 women a year. Six thousand five-hundred women died of endometrial cancer in the year 2000, representing a dramatic 224% increase in the past decade.

It is hypothesized that there are two natural history courses for endometrial cancer: Type 1, which is estrogen related, and Type 2, which is unrelated to estrogen stimulation and much more common in the United States. Type 1 is seen in younger, heavier patients, tends to be lower grade, and involves exogenous estrogen. Type 2 occurs in older and thinner women as well as those endometrial cancers that have a genetic basis, especially hereditary non-polyposis colon cancer (HNPCC).

Several constitutional factors have been identified in women who develop endometrial cancer including obesity, nulliparity, late menopause, unopposed estrogen, diabetes, and hypertension. Obesity is the greatest risk factor. Atypical endometrial hyperplasia is the pre-malignant precursor of Type 1 endometrial cancer. Virtually all of these patients, if left untreated, will develop invasive endometrial cancer over time. Fortunately, a simple hysterectomy will eliminate the chance of metastatic disease. Women with a history of breast cancer who take Tamoxifen have a slightly increased risk of endometrial cancer and uterine sarcoma. Abnormal bleeding while on this medication always prompts immediate investigation with endometrial sampling. Interestingly, Raloxifene does not increase the risk of endometrial cancer.

Over 90% of all women with endometrial cancer present with postmenopausal bleeding. There are no satisfactory ways to screen for endometrial cancer. Pap smears do not screen for endometrial cancer. However, Pap smears revealing atypical glandular cells or malignant endometrial cells frequently lead to the diagnosis of endometrial cancer. Women with postmenopausal or abnormal

perimenopausal bleeding should be evaluated with endometrial biopsy. High-risk women over 35 with menomettrhagia should also be biopsied. Ultrasound can be useful in the evaluation of abnormal bleeding. If the endometrial stripe is less than 5mm, the risk of endometrial cancer is virtually elevated. Recurrent bleeding is an indication for endometrial sampling even if an ultrasound is normal. The survival of patients with endometrial cancer is correlated with the stage of disease. Endometrial cancer is highly curable if caught early. Stage 1 disease is cured in over 90% of cases while distant disease realizes only a 10% long-term cure rate.

Surgery is the cornerstone of endometrial cancer therapy. Once a diagnosis of endometrial cancer is made, the patient should be referred to a gynecologic oncologist. With the exception of very small, early, non-invasive, grade 1 lesions, all patients should undergo a staging procedure including hysterectomy, salpingooopherectomy, and pelvic and para-aortic lymphadenectomy. If more extensive disease is found, radical resection is indicated.

Recent studies have confirmed the benefit of complete lymphadenectomy in endometrial cancer patients. In the year 2000, a University of Alabama study found an improvement in survival in even early staged patients undergoing complete lymphadenectomy. This is presumably due to the resection of clinically occult microscopic metastatic foci.

Recent publications have called into question the role of radiation therapy for patients with locally advanced endometrial cancer. A large Gynecologic Oncology Group trial (GOG 99) found no statistical improvement in survival for patients with high-risk early and locally advanced disease treated with adjuvant radiation therapy, although pelvic disease was controlled.

Advanced and recurrent endometrial cancer can be treated using several therapies, sometimes quite successfully. A current GOG trial open in Hawaii offers radiation therapy, chemotherapy with platinum, Taxol, and Adriamycin, as well as hormonal therapy with Tamoxifen and Megace.

Lower grade endometrial cancers are estrogen receptor positive and frequently have dramatic responses even with widely metastatic disease to hormonal therapy. Because of the estrogen receptors seen in endometrial cancer, hormone replacement therapy has traditionally been withheld. Retrospective studies, however, have found no detriment to survival with HRT. The GOG has an ongoing prospective randomized-blinded trial to answer definitively this very question. Patients in Hawaii diagnosed with endometrial cancer can choose to be a part of this study.

The future includes tumor biology. Gynecologic researchers have turned to molecular biology in an attempt to elucidate the etiology of these cancers. Recent research describing DNA ploidy, oncogene, and tumor suppressor gene mutations common to these malignancies is providing a basis for molecular genesis of there cancers. For example, DNA ploidy is an independent quantifiable predictor of progression-free survival in patients with endometrial cancer. Aneuploidy implies the presence of an abnormal quantity of genomic material and imparts a less favorable prognosis. The over expression of several regulatory genes, such as c-fms, K-ras, HER-2/neu, and p53, also may harbor prognostic significance in endometrial cancer. Molecular events may determine various behavioral characteristics of tumors. Therefore, the identification of molecular variables may assist clinicians in determining patient risk status and in selecting treatment options.

Beyond molecular research, reducing obesity in the United States would be an immediate way to reverse the increasing incidence of endometrial cancer. Additionally, the use of oral contraceptives in high-risk patients under 50 would dramatically lower the risk of endometrial cancer. Finally, persuading patients to seek medical attention for abnormal bleeding and encouraging physicians to perform evaluations with any signs of bleeding would go a long way toward maximizing survival.

Conclusion

As a physician and scientist, there is no better time in history to be involved in the understanding and advancement to treatment for gynecologic cancers. So much is being discovered every day. There are exciting new serum markers for the detection of early ovarian cancer, prophylactic vaccinations that could eliminate cervical cancer all together, and advances in the surgical treatment of endometrial cancer. Part of our mission is to allow our patients the opportunity to participate in potentially life-saving treatment and screening trials, many of which are available right here at home in Hawaii.